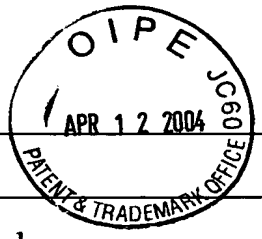


Application Number: 09/990,499

Filing Date: 11/21/2001

First Named Inventor: R. K. Bakshi, et al.

Group Art Unit: 1625

Examiner Name: D. M. Seaman

Attorney Docket Number: 20385YDA

FIRST CLASS MAIL CERTIFICATE

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VIRGINIA 22313-1450, ON THE DATE APPEARING BELOW.

MERCK & CO., INC.

MAILED BY Denise K. Brown DATE 4-9-2004

AF/1625 SH

Approved for use through 07/31/2006. OMB 0651-0032
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
SUBSTITUTE for PTO/SB/17(10-03)"FEE TRANSMITTAL for FY 2003"

OIPE
APR 12 2004
PATENT & TRADEMARK OFFICE 092

FEE TRANSMITTAL

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	$330

Complete if Known	
Application Number	09/990,499
Filing Date	November 21, 2001
First Named Inventor	R. K. Bakshi, et al.
Examiner Name	D. M. Seaman
Group Art Unit	1625
Attorney Docket Number	20385YDA

METHOD OF PAYMENT

☒ Deposit Account

Deposit Account Number: 13-2755

Deposit Account Name: Merck & Co., Inc.

The Director is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Fee Description	Fee Paid
1001	770	Utility filing fee	
1002	340	Design filing fee	
1004	770	Reissue filing fee	
1005	160	Provisional filing fee	

SUBTOTAL(1) $0

2. EXTRA CLAIM FEES

			Extra		Fee from below	Fee Paid
Total Claims		- 20 ** =	0	x	$18 =	0
Independent Claims		- 3 ** =	0	x	$86 =	0
Multiple Dependent Claims					$290 =	

***or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Fee Description
1202	18	Claims in excess of 20
1201	86	Independent claims in excess of 3
1203	290	Multiple dependent claim, if not paid
1204	86	**Reissue independent claims over original patent
1205	18	**Reissue claims in excess of 20 and over original patent

SUBTOTAL(2) $0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Fee Code	Large Entity Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1812	2,520	For filing a request for *ex parte* reexamination	
1251	110	Extension for reply within first month	
1252	420	Extension for reply within second month	
1253	950	Extension for reply within third month	
1254	1,480	Extension for reply within fourth month	
1255	2,010	Extension for reply within fifth month	
1401	330	Notice of Appeal	
1402	330	Filing a brief in support of an appeal	330
1403	290	Request for oral hearing	
1452	110	Petition to revive - unavoidable	
1453	1,330	Petition to revive - unintentional	
1501	1,330	Utility issue fee (or reissue)	
1502	480	Design issue fee	
1460	130	Petitions to the Commissioner	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	Request for Continued Examination (RCE)	
Other fee (specify)			
Other fee (specify)			

SUBTOTAL(3) $330

SUBMITTED BY

Typed or Printed Name	Melvin Winokur			Reg. Number	32,763
Signature		Date	04/09/2004	Deposit Account User ID	

IN DUPLICATE

Computer generated form "Miscellaneous Fee Sheet" (FEES Folder), Merck & Co., Inc. 10/1/2003

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS & PATENT INTERFERENCES

Applicants:	R.K. Bakshi, et al.	
Serial No.:	09/990,499 (Case No. 20385YDA)	Art Unit: 1625
Filed:	November 21, 2001	
For:	SUBSTITUTED PIPERIDINES AS MELANOCORTIN-4 RECEPTOR AGONISTS	Examiner: D. M. Seaman

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.
MERCK & CO., INC.
By Denise K Bower Date 4-9-2004

BRIEF ON APPEAL

Sir:

The present Brief is submitted in triplicate under the provisions of 37 C.F.R. 1.192 in support of an appeal from the final rejection of the above-cited application dated December 2, 2003. The Notice of Appeal was timely filed on March 1, 2004. Appellants hereby respectfully seek to have the rejections of pending Claims 39-75 overturned.

REAL PARTY IN INTEREST

The present application has been assigned to Merck & Co., Inc. of Rahway, New Jersey, by assignment recorded at the U.S. Patent and Trademark Office on January 8,

2002 (Reel 012461/Frame 0891). The inventors on the application assigned their interests to Merck & Co., Inc., in assignments executed May 23, 2000; May 24, 2000; May 25, 2000; and June 9, 2000.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellants, or known to Appellants' legal representative, that will directly affect the Board's decision in the pending appeal.

STATUS OF CLAIMS

The Claims pending as of the time of the Final Rejection are Claims 39-75, which constitute the Claims being appealed. A complete set of the Claims under appeal is provided in the accompanying Appendix.

STATUS OF AMENDMENTS

No amendment was filed in response to the Final Rejection dated December 2, 2003, of the Claims as amended under 37 C.F.R. 1.111 on September 25, 2003, in response to the Office Action dated August 26, 2003.

SUMMARY OF THE INVENTION

The present invention defined in Claims 39-73 under appeal relates to novel methods of treating male erectile dysfunction (MED) with selective agonists of the human melanocortin-4 receptor (MC-4R). Claims 74-75 are directed to methods for the oral treatment of MED with selective agonists of the human MC-4R.

ISSUES

There are two issues being presented for review by the Board of Appeals. The first issue is the rejection of Claims 39-75 as being unpatentable for failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph, and the

second issue is the rejection under 35 U.S.C. §112, first paragraph, of Claims 39-75 as being unpatentable for lack of enablement as to how to make and/or use the claimed invention. Appellants believe both rejections to be erroneous, as will be explained in the Argument Section below.

GROUPING OF CLAIMS

For the purpose of this Appeal, the Claims shall be grouped as follows:

Group I: Claims 39-73
Group II: Claims 74-75

The Claims of Groups I and II are considered to be separately patentable and do not stand or fall together. The Claims of Group I are directed to methods of treating male erectile dysfunction with selective human MC-4R agonists. The Claims of Group II are limited to methods for the oral treatment of male erectile dysfunction comprising the oral administration of a selective human MC-4R agonist.

ARGUMENT

The Claims of Group I are directed to methods of treating male erectile dysfunction by administering a therapeutically effective amount of a selective human MC-4R agonist. Since the Claims of Group II are limited to the oral treatment of male erectile dysfunction with a human MC-4R agonist, they are considered to be separately patentable from those of Group I.

As will be set forth in detail below, Appellants submit that Appellants were in possession of the claimed invention at the time the application was filed and that the Appellants' specification fully teaches one skilled in the pertinent art how to make and how to practice the claimed invention as defined in Claims 39-73 and Claims 74-75, whereby the Board of Appeals should reverse the Examiner's rejections. Favorable action by the Board is respectfully requested.

Issue 1 - Claims 39-73 and 74-75 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and they are therefore rejected under 35 U.S.C. §112, first paragraph. Appellants believe this rejection to be erroneous.

The Examiner's Rationale

The Examiner's position is that because the inventors were not in possession of the claimed invention, the claims fail to comply with the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner contends that no structural characteristics of an agonist other than compounds of formula (I) in the specification are provided by the Appellants, and the specification does not enable any person skilled in the art to choose a compound that is outside the scope of formula (I).

The §112, First Paragraph, Rejection for Lack of Written Description is Improper

The Examiner stipulates that the Appellants' specification does not provide any guidance with respect to how to choose a compound outside the scope of the instant formula (I) that would fulfill the requirements of the claims, that is, that there is no "description" of the identifying characteristics for recognizing that a compound is a candidate for the claims. The Appellants respectfully disagree with the Examiner's contention. Although the Appellants describe compounds of formula (I) as being selective MC-4R agonists, such compounds are merely representative of other structural types known in the art that may also be selective agonists. A relationship has been established in the art between the **function** of binding to the family of G-protein-coupled receptors to which MC-4R belongs and the **structure** of potential ligands having affinity for such receptors. A review of these so-called "privileged structure" based ligands of G-protein-coupled receptors was published in Annual Reports in Medicinal Chemistry, Vol. 35, pp 289-298 (2000) and is exemplified by the discovery of chemokine CCR5 antagonists described in Expert Opin. Ther. Patents, 13: 1469-1473 (2003). Thus, privileged structures and their affinity for G-protein coupled receptors were well

appreciated in the medicinal chemical arts at the time of filing of Appellants' patent application. Indeed it was Appellants' recognition of this art that led them in the first place to focus on 4-substituted piperidines of formula (I) as potential selective ligands for MC-4R. However, 4-substituted piperidines are merely one class of such privileged structure scaffolds known in the G-protein-linked receptor art. Other structurally diverse variants outside the scope of formula (I) make up a rich pool of compounds from the G-protein-linked receptor art for evaluation according to the methods described in the instant application. They include *inter alia* compounds having a 1,1-diphenylmethyl, benzodiazepine, biphenyl, tricyclic aromatic, 4-arylpiperidine and spiro versions thereof (such as spiroindanylpiperidine), 4-arylpiperazine, peptidyl, and peptidomimetic structural motif. Thus, guidance for the selection of compounds beyond those of formula (I) that would fulfill the requirements of Claims 39-75 was and continues to be provided by the art. Hence, there does exist in the art definite structural characteristics for recognizing candidate compounds with the potential to function as selective MC-4R agonists thereby providing clear guidance with respect to how to choose a compound outside the scope of formula (I).

For the above reasons, the Appellants submit that their specification contains an adequate written description of their invention, and therefore, the rejection under §112, first paragraph, should be withdrawn.

Issue 2 – Claims 39-73 and 74-75 contain subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains to make and/or use the invention, and they are therefore rejected under 35 U.S.C. §112, first paragraph. Appellants believe this rejection to be erroneous.

The Examiner's Rationale

The Examiner's position is that the specification does not enable the ordinary practitioner of the pertinent art to choose a compound other than one specifically disclosed in the subject application, namely a substituted isoquinoline of structural formula I in the specification. The Examiner contends that there is no guidance

provided as to what kind of compound to choose other than one of formula I and that extensive and undue experimentation would be required for the ordinary practitioner to randomly screen structurally undefined compounds to see if they are selective agonists of the human MC-4R according to the parameters disclosed in the Claims.

The §112, First Paragraph, Rejection for Lack of Enablement is Improper

The Examiner has misconstrued the nature of Appellants' invention. The Appellants have not invented any particular chemical compound, a class of structurally defined compounds, or methods of using a particular chemical compound or class of structurally defined compounds. Therefore, the requirements of §112, first paragraph, for enablement support for claims to specific chemical compounds or uses thereof is not relevant. Rather the Appellants have discovered a specific physiological function for the human MC-4R, that is, its central nervous system control of sexual function. They have discovered a link between MC-4R agonism and induction of penile erections, that is, that selective activation of MC-4R can induce penile erections and consequently small molecule agonists of MC-4R have therapeutic utility to treat male erectile dysfunction (MED). Briefly, the Appellants have not invented compounds, but a novel method of treating erectile dysfunction in human males. Prior to Appellants' invention, the art taught only non-selective melanocortin receptor ligands for the treatment of MED, such as the compound MT-II, and even suggested that the erectogenic properties of melanotropic compounds was "probably mediated by a receptor other than the melanocortin-4 receptor" and "this other receptor could perhaps be the melanocortin-3 receptor" [A. Vergoni, European J. Pharmacol., 362: 95-101 (1998)]. At the time the Appellants' invention was made, the MC-4R was appreciated to play an important role in the control of feeding rather than sexual behavior.

Therefore, the "critical reaction parameter" for method claims 39-73 and 74-75 is the function of selective activation of the human MC-4R. Appellants' specification clearly sets out a roadmap for the skilled artisan in the pharmacological arts to follow in order to identify compounds which bind selectively to MC-4R and which also function as agonists of MC-4R according to the parameters of Claims 39-75. The

specification then proceeds to describe how to evaluate their therapeutic properties in several *in vivo* models of MED. The methods to be used to identify selective binders of MC-4R are presented on page 35 of the specification, which describes the assays that measure binding affinities to five different melanocortin receptor subtypes. Next the methods needed to determine whether the selective binders of MC-4R also function as selective agonists of MC-4R are provided by a description of the functional assays on page 37 of the specification. These functional assays are able to discriminate MC-4R agonists from antagonists. By a selective MC-4R agonist is meant a compound that binds to MC-4R and initiates a pharmacological response characteristic of only that receptor, that is, a compound that activates MC-4R and not the other four MC-R's. The ready availability of automated methods for drug screening, such as high-throughput screening (HTS), in the pharmaceutical industry allows for the routine screening of large chemical collections and libraries of chemical compounds to identify compounds with defined biological properties, such as selective activation of human MC-4R. This type of rapid and automated screening is well within the bounds of one of ordinary skill in the art of identifying biologically active compounds and does not require "extensive and undue experimentation." In fact, such assays are now routinely performed by programmed robots and can be set up to "tag" compounds that fall within the parameters of Claims 39-75. The process is not a random one. The Federal Circuit addressed the issue of amount of experimentation in *In re Wands* [8 USPQ2d 1400] as follows:

> Enablement is not precluded by the necessity for some experimentation such as **routine screening**. However, experimentation needed to practice the invention must not be undue experimentation. [8 USPQ2d at 1404]

"A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" [*In re Wands*, 8 USPQ2d at 1404] and "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance [*In re Colianni*, 195 USPQ at 153],

which the Appellants have done in their specification. Time and difficulty of experiments are not determinative if they are merely routine (quoting from MPEP 2164.06). Wands, by its reference to routine screening as not constituting undue experimentation, clearly supports Appellants' position that the method claims of the instant invention are fully enabled.

Once the in vitro parameters of Claims 39-75 are satisfied, methods to use such MC-4R-selective agonists to treat MED are provided on pages 38-39 of the specification which describe the rat *ex copula* model of penile erection. Thus, how to identify ("make") and how to use compounds within the scope of Claims 39-75 are clearly set out in Appellants' specification. The identity of such compounds is not limited to, but is merely exemplified by, the isoquinoline compounds of the present application. Since the Appellants' specification enables the "critical or essential method parameters which are necessary to the practice of the invention," no undue experimentation is required other than carrying out what is taught in the specification. Example 84 constitutes a working example which clearly illustrates the operability of the present invention. The compound disclosed in Example 84 is representative of compounds that are selective agonists of human MC-4R within the parameters of the claims which induce penile erections in the rat when administered either by the oral or parenteral route. In short, Appellants' specification describes actual compounds suitable for use in practicing the claimed invention as well as ways of finding more such compounds whose structures can be deduced from known structure-function correlations.

Once a compound having the receptor binding and functional properties within the parameters of Claims 39-73 and 74-75 is identified, then the preparation of a pharmaceutical composition for systemic administration, as well as determining an appropriate dose and the route of administration, can be accomplished following the methods described in the instant application or modifications thereof which are known to one of ordinary skill in the pharmaceutical arts. Although some experimentation may be necessary, the pharmaceutical arts typically engage in such activity in the drug discovery process. The test of enablement is not whether any experimentation is necessary, but whether such necessary experimentation is undue

(quoting from MPEP 2164.01). Thus, the Appellants submit that one reasonably skilled in the art could make/use the present invention from the disclosures in their specification coupled with information known in the art without undue experimentation.

Since the Appellants' specification does indeed teach one of ordinary skill how to identify selective MC-4R agonists and how to use them to treat MED, the Appellants submit that the enablement contained therein is fully commensurate in scope with Claims 39-73 and 74-75.

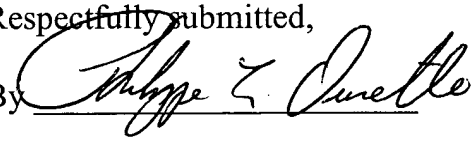
The patentability of functional claims without reference to chemical structure is supported by the consistent allowance by the U.S. Patent Office of such claims as in (a) U.S. Patent No. 6,469,012 with Claim 24 directed to a method of treating erectile dysfunction with a selective cGMP PDE-V inhibitor; (b) U.S. Patent No. 5,403,847 with claims directed to methods of treating benign prostatic hypertrophy with compounds that bind to the human α1c adrenergic receptor; (c) U.S. Patent No. 6,426,343 with claims directed to a method of enhancing cognition without producing convulsions with a compound that is a $GABA_A$ selective α5 receptor inverse agonist; (d) U.S. Patent No. 6,645,774 with claims directed to a method for treating obesity using non-peptidyl antagonists of the NPY Y5 receptor versus Y1-Y4 receptors, and (e) U.S. Patent No. 6,303,661 with claims directed to a method for lowering elevated post-prandial blood glucose levels comprising the administration of an inhibitor of dipeptidyl peptidase-IV. The level of written description and enablement provided by the patentees for the allowed functional claims in these issued U.S. patents is commensurate to that provided by the Appellants for the functional claims in the present application, that is, the Appellants' method claims 39-75 are in a breadth and format that have repeatably been found allowable by the U.S. Patent Office.

The Appellants have disclosed to the public a potentially medically useful approach for the treatment of erectile dysfunction based on a novel mechanism of action. They in turn should be granted claims that are commensurate with the significance and breadth of their invention.

SUMMARY

For the foregoing reasons, Appellants maintain that their application contains a written description of the invention in sufficient terms to allow one skilled in the art to know what was invented and thus were in possession of the claimed invention at the time the application was filed and, moreover, that their specification fully enables one skilled in the art to make and use the claimed invention without undue experimentation. It is therefore respectfully requested that the Board of Appeals reverse the Examiner's rejection of Claims 39-73 and 73-75 under 35 U.S.C. §112, first paragraph.

Respectfully submitted,

By 

Philippe L. Durette
Reg. No. 35,125
Attorney for the Appellants
Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907

Date: April 9, 2004

APPPENDIX

Appeal Claims: Application Serial No. 09/990,499

39. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human melanocortin-4 receptor (MC-4R) agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nanomolar (nM) and the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 30 nM.

40. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 100 nM.

41. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 1000 nM.

42. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 2100 nM.

43. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 30 nM.

44. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 100 nM.

45. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 540 nM.

46. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 30 nM.

47. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} of greater than 100 nM.

48. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 230 nM.

49. The method of Claim 39 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 30 nM.

50. The method of Claim 40 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 100 nM.

51. The method of Claim 41 wherein the compound is further characterized by binding to each of the human MC-2R and MC-3R with an IC_{50} greater than 540 nM and binding to the MC-5R with an IC_{50} greater than 230 nM.

52. The method of Claim 49 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 30 nM.

53. The method of Claim 50 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 100 nM.

54. The method of Claim 51 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 500 nM.

55. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

56. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

57. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 1000-fold higher than the compound binds to each of the human MC-1R and MC-2R, at least 580-fold higher than the compound binds to the human MC-3R, and at least 250-fold higher than the compound binds to the human MC-5R.

58. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to any other human melanocortin receptor.

59. The method of Claim 58 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to any other human melanocortin receptor.

60. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-1R is characterized by an EC_{50} greater than 10 nM.

61. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 100 nM.

62. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 1200 nM.

63. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-3R is characterized by an EC_{50} greater than 10 nM.

64. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 100 nM.

65. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 1200 nM.

66. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-5R is characterized by an EC_{50} greater than 10 nM.

67. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 100 nM.

68. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 520 nM.

69. The method of Claim 60 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 10 nM.

70. The method of Claim 61 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 100 nM.

71. The method of Claim 62 wherein the compound is further characterized by having a functional activity at the human MC-2R and MC-3R with an EC_{50} greater than 1200 nM and a functional activity at the human MC-5R with an EC_{50} greater than 520 nM.

72. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 10-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

73. The method of Claim 72 wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 100-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

74. A method for the oral treatment of erectile dysfunction in a male subject which comprises the oral administration to the subject in need thereof a therapeutically effective amount of a compound which is an agonist of the human MC-4R.

75. The method of Claim 74 wherein the compound is a selective agonist of the human MC-4R.

OIPE
APR 12 2004
PATENT & TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS & PATENT INTERFERENCES

Applicants:	R.K. Bakshi, et al.	
Serial No.:	09/990,499 (Case No. 20385YDA)	Art Unit: 1625
Filed:	November 21, 2001	Examiner: D. M. Seaman
For:	SUBSTITUTED PIPERIDINES AS MELANOCORTIN-4 RECEPTOR AGONISTS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

MERCK & CO., INC.
By Denise K Bauer Date 4-9-2004

BRIEF ON APPEAL

Sir:

The present Brief is submitted in triplicate under the provisions of 37 C.F.R. 1.192 in support of an appeal from the final rejection of the above-cited application dated December 2, 2003. The Notice of Appeal was timely filed on March 1, 2004. Appellants hereby respectfully seek to have the rejections of pending Claims 39-75 overturned.

REAL PARTY IN INTEREST

The present application has been assigned to Merck & Co., Inc. of Rahway, New Jersey, by assignment recorded at the U.S. Patent and Trademark Office on January 8,

2002 (Reel 012461/Frame 0891). The inventors on the application assigned their interests to Merck & Co., Inc., in assignments executed May 23, 2000; May 24, 2000; May 25, 2000; and June 9, 2000.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellants, or known to Appellants' legal representative, that will directly affect the Board's decision in the pending appeal.

STATUS OF CLAIMS

The Claims pending as of the time of the Final Rejection are Claims 39-75, which constitute the Claims being appealed. A complete set of the Claims under appeal is provided in the accompanying Appendix.

STATUS OF AMENDMENTS

No amendment was filed in response to the Final Rejection dated December 2, 2003, of the Claims as amended under 37 C.F.R. 1.111 on September 25, 2003, in response to the Office Action dated August 26, 2003.

SUMMARY OF THE INVENTION

The present invention defined in Claims 39-73 under appeal relates to novel methods of treating male erectile dysfunction (MED) with selective agonists of the human melanocortin-4 receptor (MC-4R). Claims 74-75 are directed to methods for the oral treatment of MED with selective agonists of the human MC-4R.

ISSUES

There are two issues being presented for review by the Board of Appeals. The first issue is the rejection of Claims 39-75 as being unpatentable for failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph, and the

second issue is the rejection under 35 U.S.C. §112, first paragraph, of Claims 39-75 as being unpatentable for lack of enablement as to how to make and/or use the claimed invention. Appellants believe both rejections to be erroneous, as will be explained in the Argument Section below.

GROUPING OF CLAIMS

For the purpose of this Appeal, the Claims shall be grouped as follows:

Group I: Claims 39-73
Group II: Claims 74-75

The Claims of Groups I and II are considered to be separately patentable and do not stand or fall together. The Claims of Group I are directed to methods of treating male erectile dysfunction with selective human MC-4R agonists. The Claims of Group II are limited to methods for the oral treatment of male erectile dysfunction comprising the oral administration of a selective human MC-4R agonist.

ARGUMENT

The Claims of Group I are directed to methods of treating male erectile dysfunction by administering a therapeutically effective amount of a selective human MC-4R agonist. Since the Claims of Group II are limited to the oral treatment of male erectile dysfunction with a human MC-4R agonist, they are considered to be separately patentable from those of Group I.

As will be set forth in detail below, Appellants submit that Appellants were in possession of the claimed invention at the time the application was filed and that the Appellants' specification fully teaches one skilled in the pertinent art how to make and how to practice the claimed invention as defined in Claims 39-73 and Claims 74-75, whereby the Board of Appeals should reverse the Examiner's rejections. Favorable action by the Board is respectfully requested.

Issue 1 - Claims 39-73 and 74-75 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and they are therefore rejected under 35 U.S.C. §112, first paragraph. Appellants believe this rejection to be erroneous.

The Examiner's Rationale

The Examiner's position is that because the inventors were not in possession of the claimed invention, the claims fail to comply with the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner contends that no structural characteristics of an agonist other than compounds of formula (I) in the specification are provided by the Appellants, and the specification does not enable any person skilled in the art to choose a compound that is outside the scope of formula (I).

The §112, First Paragraph, Rejection for Lack of Written Description is Improper

The Examiner stipulates that the Appellants' specification does not provide any guidance with respect to how to choose a compound outside the scope of the instant formula (I) that would fulfill the requirements of the claims, that is, that there is no "description" of the identifying characteristics for recognizing that a compound is a candidate for the claims. The Appellants respectfully disagree with the Examiner's contention. Although the Appellants describe compounds of formula (I) as being selective MC-4R agonists, such compounds are merely representative of other structural types known in the art that may also be selective agonists. A relationship has been established in the art between the **function** of binding to the family of G-protein-coupled receptors to which MC-4R belongs and the **structure** of potential ligands having affinity for such receptors. A review of these so-called "privileged structure" based ligands of G-protein-coupled receptors was published in Annual Reports in Medicinal Chemistry, Vol. 35, pp 289-298 (2000) and is exemplified by the discovery of chemokine CCR5 antagonists described in Expert Opin. Ther. Patents, 13: 1469-1473 (2003). Thus, privileged structures and their affinity for G-protein coupled receptors were well

appreciated in the medicinal chemical arts at the time of filing of Appellants' patent application. Indeed it was Appellants' recognition of this art that led them in the first place to focus on 4-substituted piperidines of formula (I) as potential selective ligands for MC-4R. However, 4-substituted piperidines are merely one class of such privileged structure scaffolds known in the G-protein-linked receptor art. Other structurally diverse variants outside the scope of formula (I) make up a rich pool of compounds from the G-protein-linked receptor art for evaluation according to the methods described in the instant application. They include *inter alia* compounds having a 1,1-diphenylmethyl, benzodiazepine, biphenyl, tricyclic aromatic, 4-arylpiperidine and spiro versions thereof (such as spiroindanylpiperidine), 4-arylpiperazine, peptidyl, and peptidomimetic structural motif. Thus, guidance for the selection of compounds beyond those of formula (I) that would fulfill the requirements of Claims 39-75 was and continues to be provided by the art. Hence, there does exist in the art definite structural characteristics for recognizing candidate compounds with the potential to function as selective MC-4R agonists thereby providing clear guidance with respect to how to choose a compound outside the scope of formula (I).

For the above reasons, the Appellants submit that their specification contains an adequate written description of their invention, and therefore, the rejection under §112, first paragraph, should be withdrawn.

Issue 2 – Claims 39-73 and 74-75 contain subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains to make and/or use the invention, and they are therefore rejected under 35 U.S.C. §112, first paragraph. Appellants believe this rejection to be erroneous.

The Examiner's Rationale

The Examiner's position is that the specification does not enable the ordinary practitioner of the pertinent art to choose a compound other than one specifically disclosed in the subject application, namely a substituted isoquinoline of structural formula I in the specification. The Examiner contends that there is no guidance

provided as to what kind of compound to choose other than one of formula I and that extensive and undue experimentation would be required for the ordinary practitioner to randomly screen structurally undefined compounds to see if they are selective agonists of the human MC-4R according to the parameters disclosed in the Claims.

The §112, First Paragraph, Rejection for Lack of Enablement is Improper

The Examiner has misconstrued the nature of Appellants' invention. The Appellants have not invented any particular chemical compound, a class of structurally defined compounds, or methods of using a particular chemical compound or class of structurally defined compounds. Therefore, the requirements of §112, first paragraph, for enablement support for claims to specific chemical compounds or uses thereof is not relevant. Rather the Appellants have discovered a specific physiological function for the human MC-4R, that is, its central nervous system control of sexual function. They have discovered a link between MC-4R agonism and induction of penile erections, that is, that selective activation of MC-4R can induce penile erections and consequently small molecule agonists of MC-4R have therapeutic utility to treat male erectile dysfunction (MED). Briefly, the Appellants have not invented compounds, but a novel method of treating erectile dysfunction in human males. Prior to Appellants' invention, the art taught only non-selective melanocortin receptor ligands for the treatment of MED, such as the compound MT-II, and even suggested that the erectogenic properties of melanotropic compounds was "probably mediated by a receptor other than the melanocortin-4 receptor" and "this other receptor could perhaps be the melanocortin-3 receptor" [A. Vergoni, European J. Pharmacol., 362: 95-101 (1998)]. At the time the Appellants' invention was made, the MC-4R was appreciated to play an important role in the control of feeding rather than sexual behavior.

Therefore, the "critical reaction parameter" for method claims 39-73 and 74-75 is the function of selective activation of the human MC-4R. Appellants' specification clearly sets out a roadmap for the skilled artisan in the pharmacological arts to follow in order to identify compounds which bind selectively to MC-4R and which also function as agonists of MC-4R according to the parameters of Claims 39-75. The

specification then proceeds to describe how to evaluate their therapeutic properties in several *in vivo* models of MED. The methods to be used to identify selective binders of MC-4R are presented on page 35 of the specification, which describes the assays that measure binding affinities to five different melanocortin receptor subtypes. Next the methods needed to determine whether the selective binders of MC-4R also function as selective agonists of MC-4R are provided by a description of the functional assays on page 37 of the specification. These functional assays are able to discriminate MC-4R agonists from antagonists. By a selective MC-4R agonist is meant a compound that binds to MC-4R and initiates a pharmacological response characteristic of only that receptor, that is, a compound that activates MC-4R and not the other four MC-R's. The ready availability of automated methods for drug screening, such as high-throughput screening (HTS), in the pharmaceutical industry allows for the routine screening of large chemical collections and libraries of chemical compounds to identify compounds with defined biological properties, such as selective activation of human MC-4R. This type of rapid and automated screening is well within the bounds of one of ordinary skill in the art of identifying biologically active compounds and does not require "extensive and undue experimentation." In fact, such assays are now routinely performed by programmed robots and can be set up to "tag" compounds that fall within the parameters of Claims 39-75. The process is not a random one. The Federal Circuit addressed the issue of amount of experimentation in *In re Wands* [8 USPQ2d 1400] as follows:

> Enablement is not precluded by the necessity for some experimentation such as **routine screening**. However, experimentation needed to practice the invention must not be undue experimentation. [8 USPQ2d at 1404]

"A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" [*In re Wands*, 8 USPQ2d at 1404] and "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance [*In re Colianni*, 195 USPQ at 153],

which the Appellants have done in their specification. Time and difficulty of experiments are not determinative if they are merely routine (quoting from MPEP 2164.06). Wands, by its reference to routine screening as not constituting undue experimentation, clearly supports Appellants' position that the method claims of the instant invention are fully enabled.

Once the in vitro parameters of Claims 39-75 are satisfied, methods to use such MC-4R-selective agonists to treat MED are provided on pages 38-39 of the specification which describe the rat *ex copula* model of penile erection. Thus, how to identify ("make") and how to use compounds within the scope of Claims 39-75 are clearly set out in Appellants' specification. The identity of such compounds is not limited to, but is merely exemplified by, the isoquinoline compounds of the present application. Since the Appellants' specification enables the "critical or essential method parameters which are necessary to the practice of the invention," no undue experimentation is required other than carrying out what is taught in the specification. Example 84 constitutes a working example which clearly illustrates the operability of the present invention. The compound disclosed in Example 84 is representative of compounds that are selective agonists of human MC-4R within the parameters of the claims which induce penile erections in the rat when administered either by the oral or parenteral route. In short, Appellants' specification describes actual compounds suitable for use in practicing the claimed invention as well as ways of finding more such compounds whose structures can be deduced from known structure-function correlations.

Once a compound having the receptor binding and functional properties within the parameters of Claims 39-73 and 74-75 is identified, then the preparation of a pharmaceutical composition for systemic administration, as well as determining an appropriate dose and the route of administration, can be accomplished following the methods described in the instant application or modifications thereof which are known to one of ordinary skill in the pharmaceutical arts. Although some experimentation may be necessary, the pharmaceutical arts typically engage in such activity in the drug discovery process. The test of enablement is not whether any experimentation is necessary, but whether such necessary experimentation is undue

(quoting from MPEP 2164.01). Thus, the Appellants submit that one reasonably skilled in the art could make/use the present invention from the disclosures in their specification coupled with information known in the art without undue experimentation.

Since the Appellants' specification does indeed teach one of ordinary skill how to identify selective MC-4R agonists and how to use them to treat MED, the Appellants submit that the enablement contained therein is fully commensurate in scope with Claims 39-73 and 74-75.

The patentability of functional claims without reference to chemical structure is supported by the consistent allowance by the U.S. Patent Office of such claims as in (a) U.S. Patent No. 6,469,012 with Claim 24 directed to a method of treating erectile dysfunction with a selective cGMP PDE-V inhibitor; (b) U.S. Patent No. 5,403,847 with claims directed to methods of treating benign prostatic hypertrophy with compounds that bind to the human α1c adrenergic receptor; (c) U.S. Patent No. 6,426,343 with claims directed to a method of enhancing cognition without producing convulsions with a compound that is a $GABA_A$ selective α5 receptor inverse agonist; (d) U.S. Patent No. 6,645,774 with claims directed to a method for treating obesity using non-peptidyl antagonists of the NPY Y5 receptor versus Y1-Y4 receptors, and (e) U.S. Patent No. 6,303,661 with claims directed to a method for lowering elevated post-prandial blood glucose levels comprising the administration of an inhibitor of dipeptidyl peptidase-IV. The level of written description and enablement provided by the patentees for the allowed functional claims in these issued U.S. patents is commensurate to that provided by the Appellants for the functional claims in the present application, that is, the Appellants' method claims 39-75 are in a breadth and format that have repeatably been found allowable by the U.S. Patent Office.

The Appellants have disclosed to the public a potentially medically useful approach for the treatment of erectile dysfunction based on a novel mechanism of action. They in turn should be granted claims that are commensurate with the significance and breadth of their invention.

SUMMARY

For the foregoing reasons, Appellants maintain that their application contains a written description of the invention in sufficient terms to allow one skilled in the art to know what was invented and thus were in possession of the claimed invention at the time the application was filed and, moreover, that their specification fully enables one skilled in the art to make and use the claimed invention without undue experimentation. It is therefore respectfully requested that the Board of Appeals reverse the Examiner's rejection of Claims 39-73 and 73-75 under 35 U.S.C. §112, first paragraph.

Respectfully submitted,

By _____

Philippe L. Durette
Reg. No. 35,125
Attorney for the Appellants
Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907

Date: April 9, 2004

APPPENDIX

Appeal Claims: Application Serial No. 09/990,499

39. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human melanocortin-4 receptor (MC-4R) agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nanomolar (nM) and the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 30 nM.

40. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 100 nM.

41. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 1000 nM.

42. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 2100 nM.

43. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 30 nM.

44. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 100 nM.

45. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 540 nM.

46. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 30 nM.

47. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} of greater than 100 nM.

48. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 230 nM.

49. The method of Claim 39 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 30 nM.

50. The method of Claim 40 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 100 nM.

51. The method of Claim 41 wherein the compound is further characterized by binding to each of the human MC-2R and MC-3R with an IC_{50} greater than 540 nM and binding to the MC-5R with an IC_{50} greater than 230 nM.

52. The method of Claim 49 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 30 nM.

53. The method of Claim 50 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 100 nM.

54. The method of Claim 51 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 500 nM.

55. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

56. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

57. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 1000-fold higher than the compound binds to each of the human MC-1R and MC-2R, at least 580-fold higher than the compound binds to the human MC-3R, and at least 250-fold higher than the compound binds to the human MC-5R.

58. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to any other human melanocortin receptor.

59. The method of Claim 58 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to any other human melanocortin receptor.

60. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-1R is characterized by an EC_{50} greater than 10 nM.

61. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 100 nM.

62. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 1200 nM.

63. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-3R is characterized by an EC_{50} greater than 10 nM.

64. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 100 nM.

65. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 1200 nM.

66. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-5R is characterized by an EC_{50} greater than 10 nM.

67. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 100 nM.

68. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 520 nM.

69. The method of Claim 60 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 10 nM.

70. The method of Claim 61 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 100 nM.

71. The method of Claim 62 wherein the compound is further characterized by having a functional activity at the human MC-2R and MC-3R with an EC_{50} greater than 1200 nM and a functional activity at the human MC-5R with an EC_{50} greater than 520 nM.

72. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 10-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

73. The method of Claim 72 wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 100-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

74. A method for the oral treatment of erectile dysfunction in a male subject which comprises the oral administration to the subject in need thereof a therapeutically effective amount of a compound which is an agonist of the human MC-4R.

75. The method of Claim 74 wherein the compound is a selective agonist of the human MC-4R.